Reverse Engineer Sample Sizes for NIH Trial

David Darmon

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Sample Size Using STAT Article

https://www.statnews.com/2020/05/11/inside-the-nihs-controversial-decision-to-stop-its-big-remdesivir-study/

Assume 606 recovered

8% in Remdesivir arm died, and 11.6% in control arm died.

Let n_1 and n_2 be the number in the control and remdesivir arms of the clinical trial, respectively. Then that means we know

$$0.884 \cdot n_1 + 0.92 \cdot n_2 = 606$$

The P-value is 0.059, so we will find (n_1, n_2) such that $p(z) = 0.059$ subject to the constraint that $0.884 \cdot n_1 + 0.92 \cdot n_2 = 480$, i.e. that

$$n_2 = \frac{606 - 0.884 \cdot n_1}{0.92}.$$

```
# num.survived <- 480
num.survived <- 606
```

P-value Assumption

Use a P-value based on the Z-statistic for a large sample test of two proportions with pooling:

$$Z_p = \frac{(\hat{p}_1 - \hat{p}_2) - \delta}{\sqrt{\hat{p}(1 - \hat{p})\left(\frac{1}{n_1} + \frac{1}{n_2}\right)}} \dot{\sim} N(0, 1)$$

where $\hat{p} = \frac{x_1 + x_2}{n_1 + n_2}$ is the proportion that died in all arms.

I also tried the unpooled Z-statistic,

$$Z = \frac{(\hat{p}_1 - \hat{p}_2) - \delta}{\sqrt{\frac{\hat{p}_1(1 - \hat{p}_1)}{n_1} + \frac{\hat{p}_2(1 - \hat{p}_2)}{n_2}}} \dot{\sim} N(0, 1).$$

That gives similar results.

```
pval <- function(n1, alternative = 'two.sided', is.pooled = TRUE, use.prop.test = TRUE){
  n2 <- (num.survived-0.884*n1)/0.92

  x1 <- 0.116*n1
  x2 <- 0.08*n2

  p1 <- x1/n1; p2 <- x2/n2
```

```r
  p <- (x1 + x2)/(n1 + n2)

  if (use.prop.test){
    prop.test(c(x1, x2), c(n1, n2), alternative = alternative)$p.value
  }else{
    if (is.pooled){
      num <- (p1 - p2)
      denom <- sqrt(p*(1-p)*(1/n1 + 1/n2))
    }else{
      num <- (p1 - p2)
      denom <- sqrt(p1*(1-p1)/n1 + p2*(1-p2)/n2)
    }

    z <- num/denom

    if (alternative == 'two.sided'){
      pval <- 2*pnorm(-abs(z))
    }else if (alternative == 'less'){
      pval <- pnorm(z)
    }else if (alternative == 'greater'){
      pval <- pnorm(z, lower.tail = FALSE)
    }
  }
}
```

Find sample sizes that give P-value

Graph showing method

```r
is.pooled <- TRUE
# is.pooled <- FALSE

# alternative <- 'two.sided'
alternative <- 'greater'

use.prop.test <- FALSE
# use.prop.test <- TRUE

pval <- Vectorize(pval, vectorize.args = 'n1')

interval <- c(325, 400)

curve(pval(x, alternative = alternative, is.pooled = is.pooled, use.prop.test = use.prop.test), from = 
      xlab = expression(italic(n)[1]), ylab = expression(italic(p)(italic(n)[1])))
abline(h = 0.059)
abline(v = interval[1], lty = 3)
abline(v = interval[2], lty = 3)
```
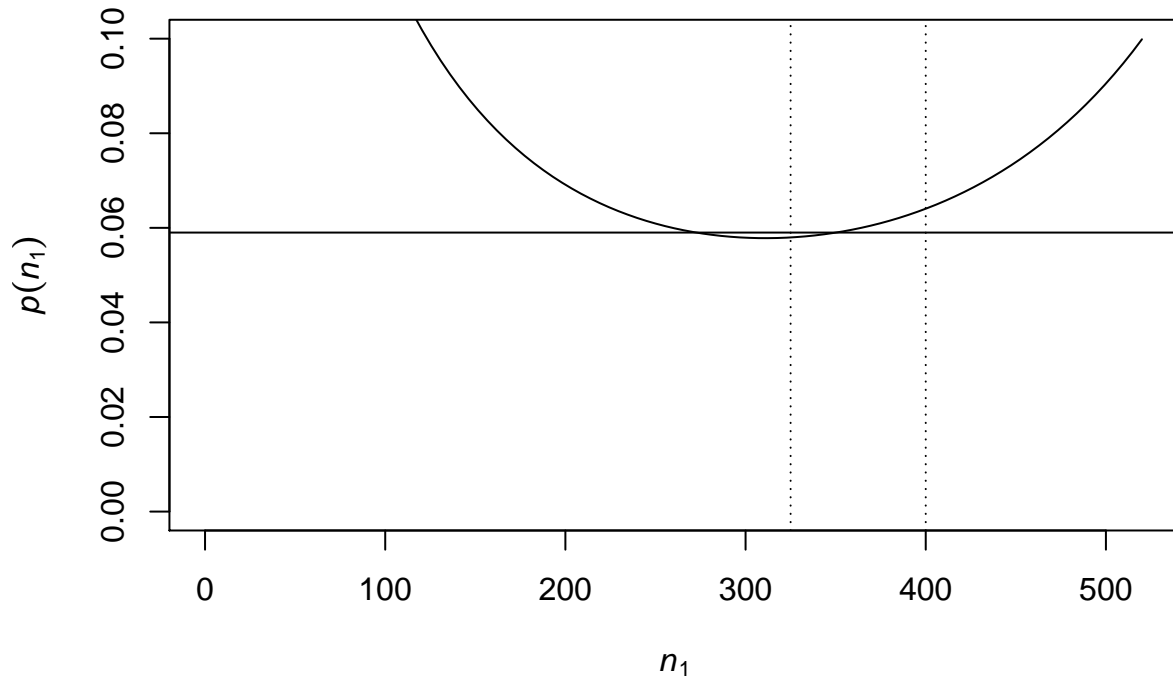
Finding the first root, since it gives a more balanced design between the two arms.

Find Root

Numerically find the root of $p(n_1) - 0.059 = 0$

```
opt.out <- uniroot(function(n1)
  pval(n1, alternative = alternative, is.pooled = is.pooled, use.prop.test = use.prop.test) - 0.059,
  interval = interval)
```

Number in control arm:

```
(n1 <- opt.out$root)
```

```
## [1] 350.1839
```

Number in remdesivir arm:

```
(n2 <- (num.survived-0.884*n1)/0.92)
```

```
## [1] 322.2146
```

Total in both arms:

```
(n.tot <- n1 + n2)
```

```
## [1] 672.3985
```

Deaths in each arm:

```
(x1 <- 0.116*n1)
```

```
## [1] 40.62133
```

```
(x2 <- 0.08*n2)
```

```
## [1] 25.77717
```

Total survivors. Should be 606 (sanity check):

```r
(n1 - x1) + (n2 - x2)
```

```
## [1] 606
```

Proportion died in each arm, should be 11.6% and 8% (another sanity check):

```r
(p1 <- x1/n1)
```

```
## [1] 0.116
```

```r
(p2 <- x2/n2)
```

```
## [1] 0.08
```

Comparison to R's Right-sided P-value

```r
(test.out <- prop.test(c(x1, x2), c(n1, n2), alternative = alternative, correct = FALSE))
```

```
##
##  2-sample test for equality of proportions without continuity
##  correction
##
## data:  c(x1, x2) out of c(n1, n2)
## X-squared = 2.4437, df = 1, p-value = 0.059
## alternative hypothesis: greater
## 95 percent confidence interval:
##  -0.001553424  1.000000000
## sample estimates:
## prop 1 prop 2
##  0.116  0.080
```

Two-sided 95% Confidence Interval for Difference in Mortality Rate

```r
prop.test(c(x1, x2), c(n1, n2))
```

```
##
##  2-sample test for equality of proportions with continuity correction
##
## data:  c(x1, x2) out of c(n1, n2)
## X-squared = 2.0559, df = 1, p-value = 0.1516
## alternative hypothesis: two.sided
## 95 percent confidence interval:
##  -0.01172725  0.08372725
## sample estimates:
## prop 1 prop 2
##  0.116  0.080
```

Large Sample Confidence Distribution

$$(\hat{p}_1 - \hat{p}_2) \pm z_{\alpha/2} \sqrt{\frac{\hat{p}_1 (1 - \hat{p}_1)}{n_1} + \frac{\hat{p}_2 (1 - \hat{p}_2)}{n_2}}$$

$$\frac{\delta - (\hat{p}_1 - \hat{p}_2)}{\sqrt{\frac{\hat{p}_1(1-\hat{p}_1)}{n_1} + \frac{\hat{p}_2(1-\hat{p}_2)}{n_2}}} \dot\sim N(0,1)$$
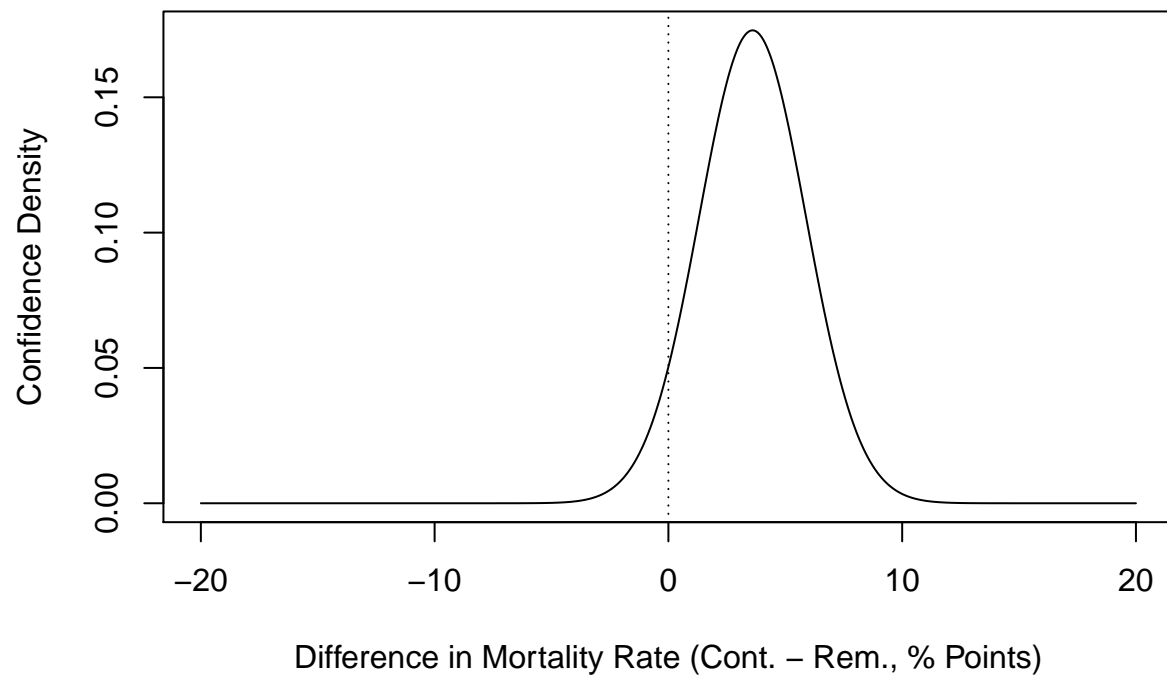
i.e.

$$\delta \text{ " } \sim \text{ " } N \left(\hat{p}_1 - \hat{p}_2, \frac{\hat{p}_1 \left(1 - \hat{p}_1 \right)}{n_1} + \frac{\hat{p}_2 \left(1 - \hat{p}_2 \right)}{n_2} \right)$$

```
delta.hat <- (p1 - p2)*100

delta.se <- sqrt(p1*(1-p1)/n1 + p2*(1-p2)/n2)*100
```
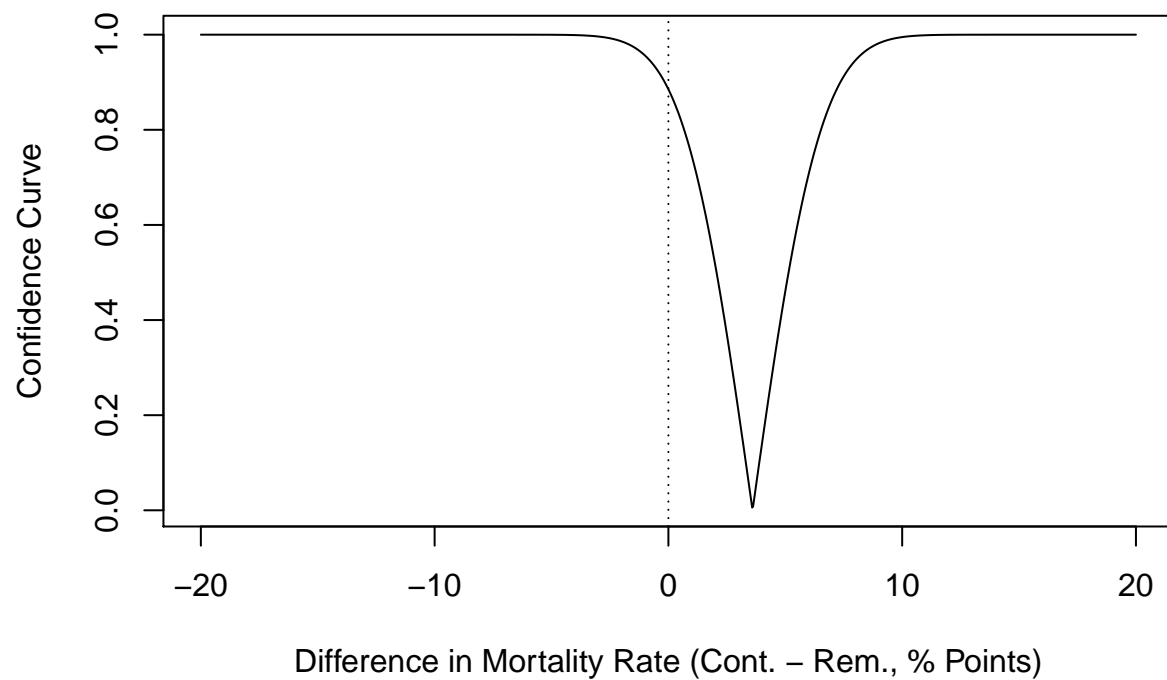
Confidence Density

```
from.to <- 20

curve(dnorm(x, delta.hat, delta.se),
      xlab = 'Difference in Mortality Rate (Cont. - Rem., % Points)',
      ylab = 'Confidence Density', xlim = c(-from.to, from.to), n = 1000)
abline(v = 0, lty = 3)
```


Difference in Mortality Rate (Cont. – Rem., % Points)

Confidence Curve

```
curve(abs(2*pnorm(x, delta.hat, delta.se)-1),
      xlab = 'Difference in Mortality Rate (Cont. - Rem., % Points)',
      ylab = 'Confidence Curve',
      xlim = c(-from.to, from.to), n = 1000)
abline(v = 0, lty = 3)
```

Severity Curve

```r
curve(1-pnorm(x, delta.hat, delta.se),
    xlab = 'Difference in Mortality Rate (Cont. - Rem., % Points)',
    ylab = 'Severity Curve',
    xlim = c(-from.to, from.to), n = 1000)
abline(v = 0, lty = 3)
```